

Carey & Sundberg Chapter 13.1 problems # 1; 2; 3a, b, c ;

Smith: Chapter 7

Protecting Groups

T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis (2nd edition) J. Wiley & Sons, 1991.

P. J. Kocienski, Protecting Groups, Georg Thieme Verlag, 1994

1. Hydroxyl groups
2. Ketones and aldehydes
3. Amines
4. Carboxylic Acids

- Protect functional groups which may be incompatible with a set of reaction conditions

- 2 step process- must be efficient

- Selectivity
- a. selective protection
 - b. selective deprotection

Hydroxyl Protecting Groups

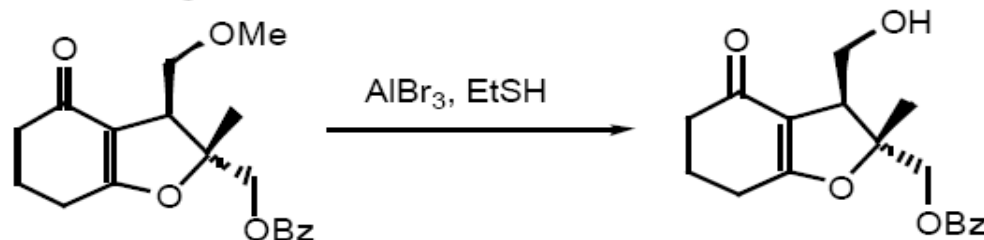
Ethers

Methyl ethers

R-OH \rightarrow R-OMe difficult to remove except for on phenols

Formation: - CH_2N_2 , silica or HBF_4
- NaH, MeI, THF

Cleavage: - AlBr_3 , EtSH
- PhSe -
- Ph_2P -
- Me_3SiI



Methoxymethyl ether MOM

R-OH \rightarrow R-OCH₂OMe stable to base and mild acid

Formation: - MeOCH_2Cl , NaH, THF
- MeOCH_2Cl , CH_2Cl_2 , $i\text{Pr}_2\text{EtN}$

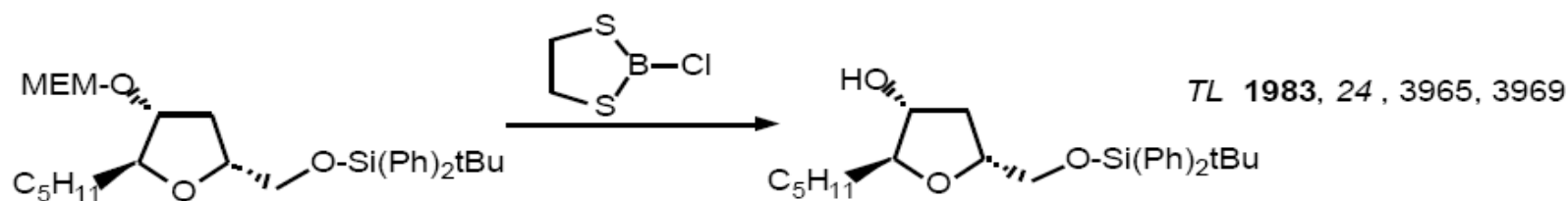
Cleavage - Me_2BBr_2 TL 1983, 24, 3969

Methoxyethoxymethyl ethers (MEM)

R-OH \rightarrow R-OCH₂OCH₂CH₂OMe stable to base and mild acid

Formation: - MeOCH₂CH₂OCH₂Cl, NaH, THF
- MeOCH₂CH₂OCH₂Cl, CH₂Cl₂, iPr₂EtN TL 1976, 809

Cleavage - Lewis acids such as ZnBr₂, TiCl₄, Me₂BBr₂



- can also be cleaved in the presence of THP ethers

Methyl Thiomethyl Ethers (MTM)

R-OH \rightarrow R-OCH₂SMe Stable to base and mild acid

Formation: - MeSCH₂Cl, NaH, THF

Cleavage: - HgCl₂, CH₃CN/H₂O
- AgNO₃, THF, H₂O, base

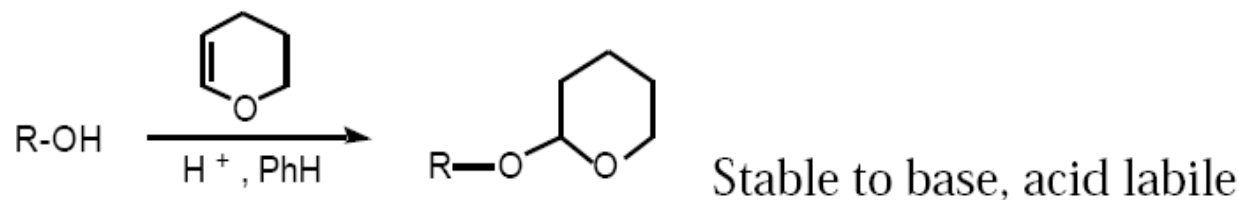
Benzyloxymethyl Ethers (BOM)

R-OH \rightarrow R-OCH₂OCH₂Ph Stable to acid and base

Formation: - PhOCH₂CH₂Cl, CH₂Cl₂, iPr₂EtN

Cleavage: - H₂/ PtO₂
- Na/ NH₃, EtOH

Tetrahydropyranyl Ether (THP)

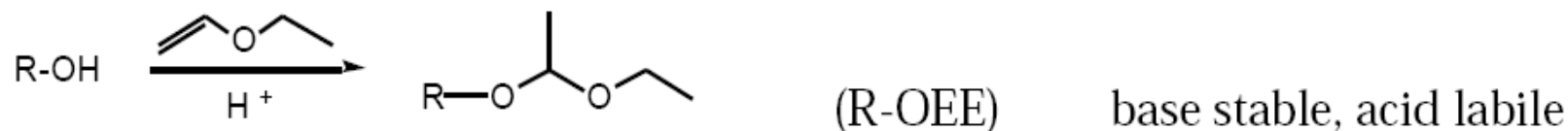


Formation - DHP (dihydropyran), pTSA, PhH

Cleavage: - AcOH, THF, H₂O
- Amberlyst H-15, MeOH

Ethoxyethyl ethers (EE)

JACS **1979**, 101, 7104; JACS **1974**, 96, 4745.



Benzyl Ethers (R-OBn)



Formation: - KH, THF, PhCH₂Cl
- PhCH₂OC(=NH)CCl₃, F₃CSO₃H JCS P1 **1985**, 2247

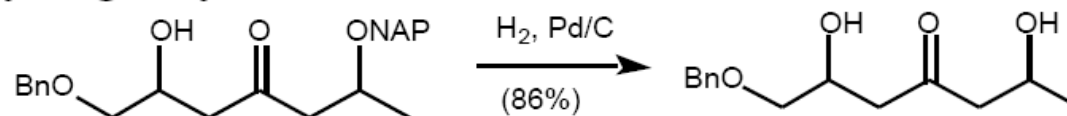
Cleavage: - H₂ / PtO₂
- Li / NH₃

2-Naphthylmethyl Ethers (NAP)

JOC **1998**, 63, 4172

formation: 2-chloromethylnapthalene, KH

cleavage: hydrogenolysis


p-Methoxybenzyl Ethers (PMB)

(PMB)

Formation:

 - KH, THF, *p*-MeOPhCH₂Cl

 - *p*-MeOPhCH₂OC(=NH)CCl₃, F₃CSO₃H

TL **1988**, 29, 4139

Cleavage:

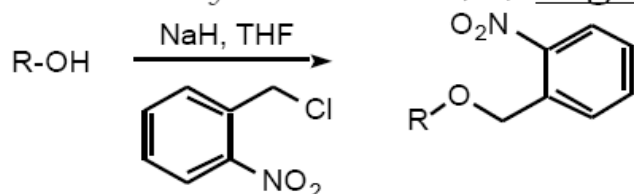
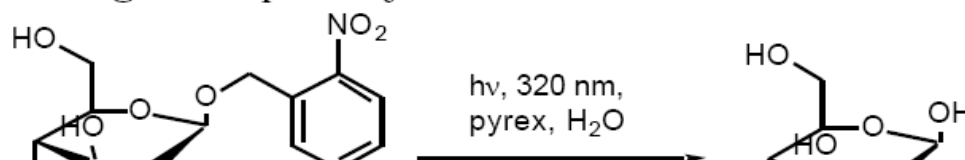
 - H₂ / PtO₂

 - Li / NH₃

- DDQ

 - Ce(NH₄)₂(NO₃)₆ (CAN)

 - e⁻
o-Nitrobenzyl ethers

 Review: *Synthesis* **1980**, 1; *Organic Photochemistry*, **1987**, 9, 225

Cleavage: - photolysis at 320 nm


p-Nitrobenzyl Ether

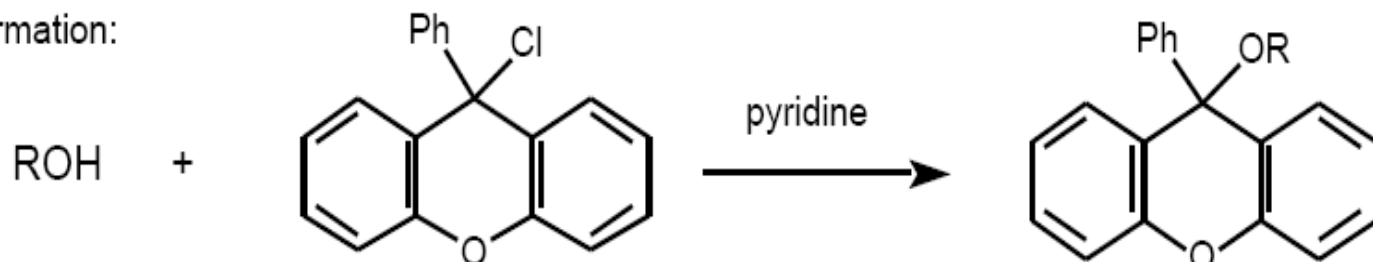
TL 1990, 31, 389

-selective removal with DDQ, hydrogenolysis or electrochemically

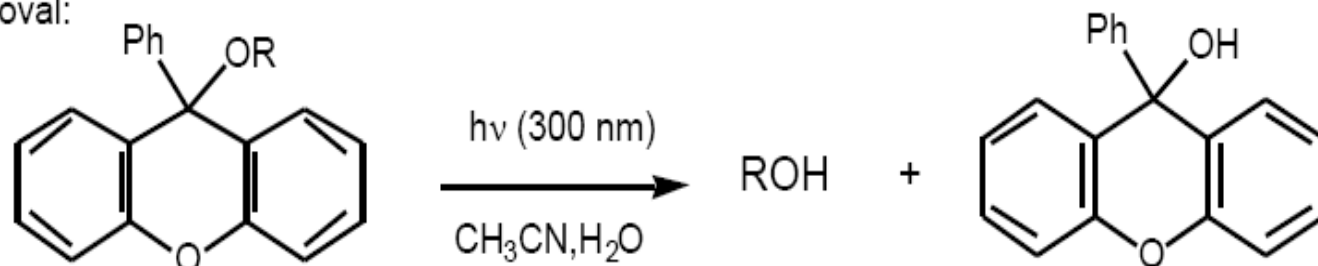
9-Phenylxanthy- (pixyl, px)

TL 1998, 39, 1653

Formation:



Removal:



*T*riyl Ethers

-CPh₃ = Tr

R-OH \rightarrow R-OCPh₃

- selective for 1° alcohols

- removed with mild acid; base stable

formation: - Ph₃C-Cl, pyridine, DMAP

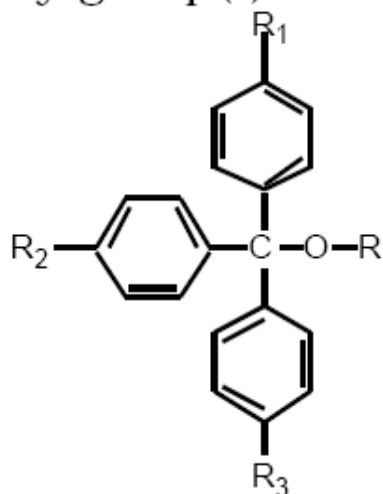
- Ph₃C⁺ BF₄⁻

Cleavage: - mild acid

Methoxytrityl Ethers

JACS 1962, 84, 430

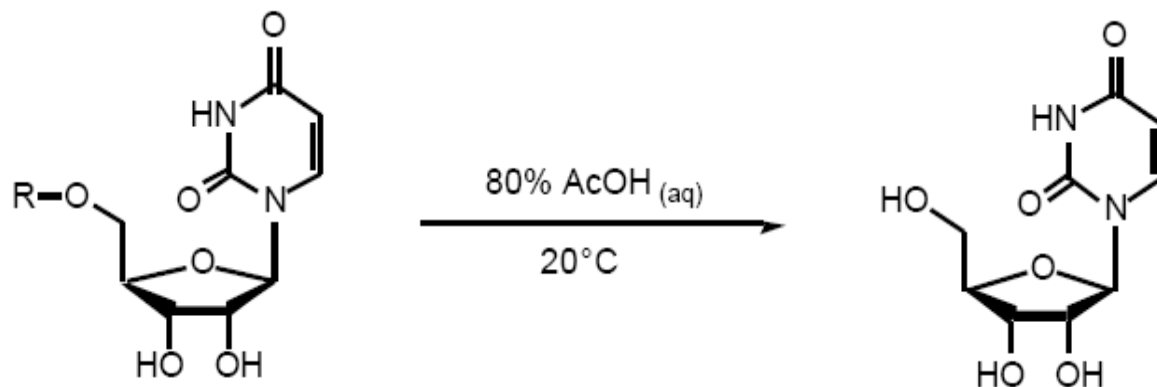
- methoxy group(s) make it easier to remove



(p-Methoxyphenyl)diphenylmethyl ether
4'-methoxytrityl MTr-OR

Di-(p-methoxyphenyl)phenylmethyl ether
4',4'-dimethoxytrityl DMTr-OR

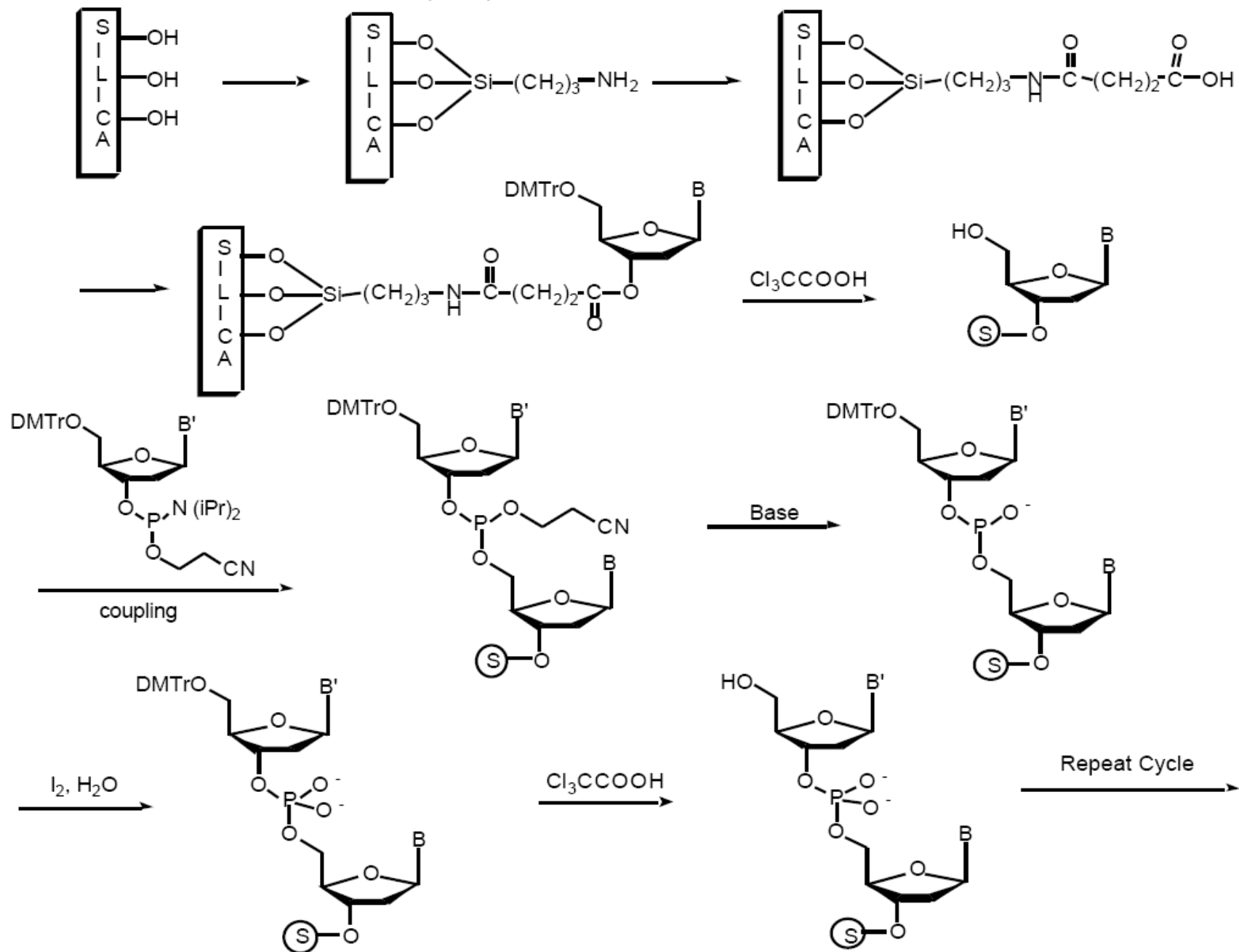
Tri-(p-methoxyphenyl)methyl ether
4',4',4'-trimethoxytrityl TMT-OR

$$\text{Tr-OR} < \text{MTr-OR} < \text{DMTr-OR} \ll \text{TMT-OR}$$


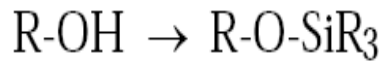
R = Tr 48 hr.
R = MTr 2 hr.
R = DMTr 15 min.
R = TMT 1 min. (too labile to be useful)

Oligonucleotide Synthesis (phosphoramidite method - Lessinger)

Review: *Tetrahedron* **1992**, *48*, 2223



Silyl Ethers *Synthesis* **1985**, 817 *Synthesis* **1993**, 11 *Synthesis* **1996**, 1031



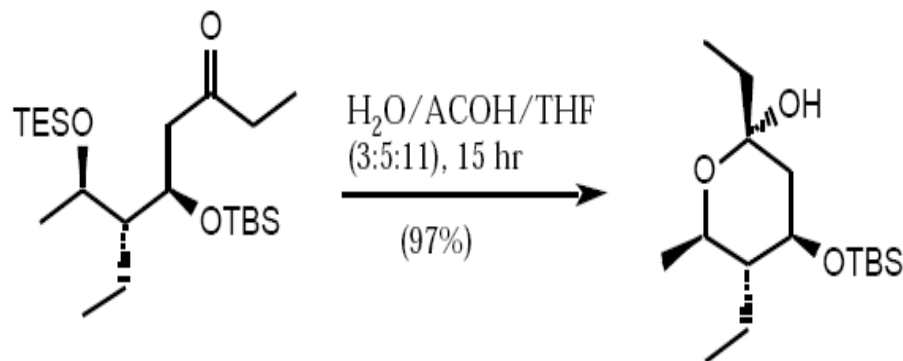
- formation:
- R₃Si-Cl, pyridine, DMAP
 - R₃Si-Cl, CH₂Cl₂ (DMF, CH₃CN), imidazole, DMAP
 - R₃Si-OTf, iPr₂EtN, CH₂Cl₂

Trimethylsilyl ethers Me₃Si-OR TMS-OR

- very acid and water labile
- useful for transient protection

Triethylsilyl ethers Et₃Si-OR TES-OR

- considerably more stable than TMS
- can be selectively removed in the presence of more robust silyl ethers with F⁻ or mild acid



Liebigs Ann. Chem. **1986**, 1281

Triisopropylsilyl ethers iPr_3Si-OR TIPS-OR
- more stable to hydrolysis than TMS

Phenyldimethylsilyl ethers

J. Org. Chem. **1987**, 52, 165

t-Butyldimethylsilyl Ether $tBuMe_2Si-OR$ TBS-OR TBDMS-OR
JACS **1972**, 94, 6190

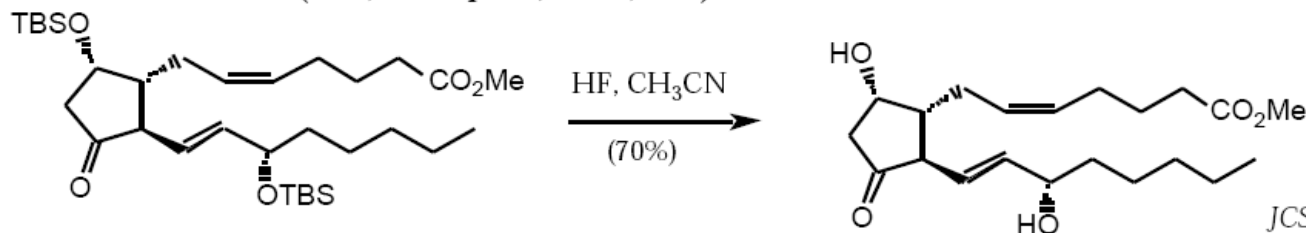
- Stable to base and mild acid
- under controlled condition is selective for 1° alcohols

t-butyldimethylsilyl triflate $tBuMe_2Si-OTf$ *TL* **1981**, 22, 3455

- very reactive silylating reagent, will silylate 2° alcohols

cleavage:

- acid
- F^- (HF, nBu_4NF , CsF, KF)



JCS Perkin Trans. 1 **1981**, 2055

t-Butyldiphenylsilyl Ether $tBuPh_2Si-OR$ TBDPS-OR Σ -OR

- stable to acid and base
- selective for 1° alcohols
- Me_3Si- and iPr_3Si groups can be selectively removed in the presence of TBS or TBDPS groups.
- TBS can be selectively removed in the presence of TBDPS by acid hydrolysis.

TL **1989**, 30, 19

cleavage - F-

- Fluoride sources: - $n\text{Bu}_4\text{NF}$ (basic reagent)

- $\text{HF} / \text{H}_2\text{O} / \text{CH}_3\text{CN}$

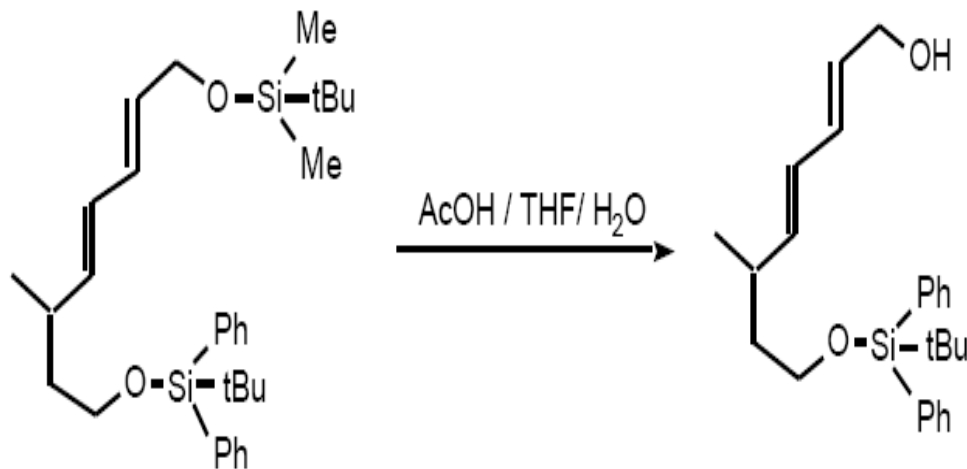
- $\text{HF} \cdot \text{pyridine}$

- $\text{SiF}_4 \cdot \text{CH}_2\text{Cl}_2$

TL **1979**, 3981.

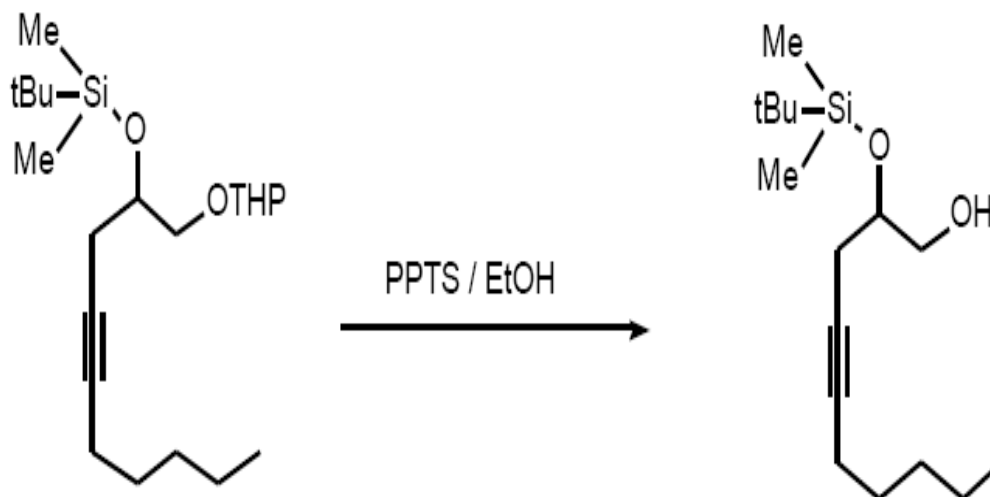
Synthesis **1986**, 453

TL **1992**, 33 , 2289



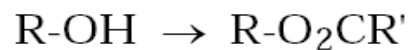
JOC **1981**, 46 ,1506

TL **1989**, 30 , 19.



JACS **1984**, 106 , 3748

Esters

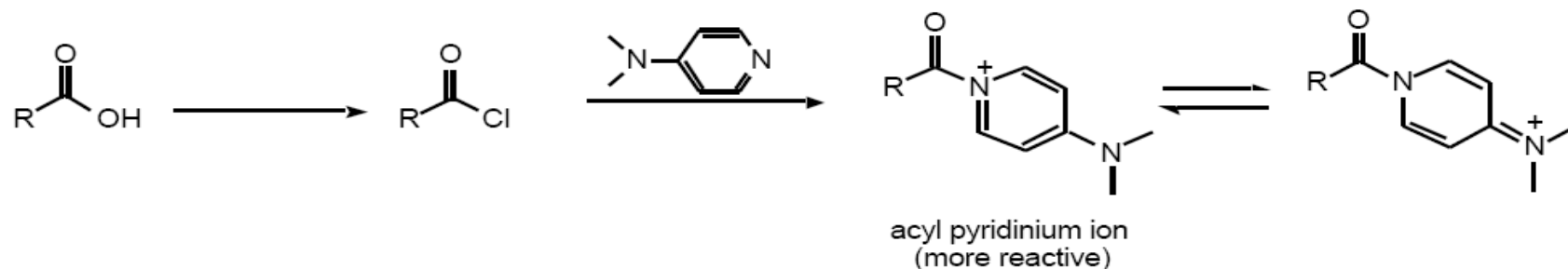


Formation: - "activated acid", base, solvent, (DMAP)

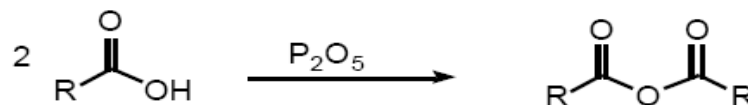
Activated Acids *Chem. Soc. Rev.* **1983**, 12, 129 *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 569.

$\text{RCO}_2\text{H} \rightarrow$ "activated acid" \rightarrow carboxylic acid derivative (ester, amide, etc.)

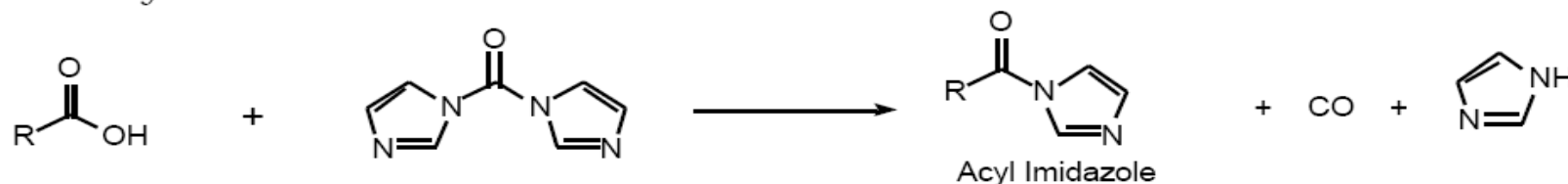
Acid Chlorides



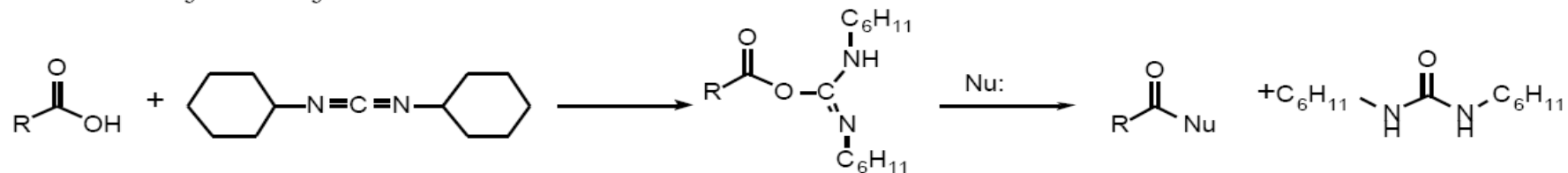
Anhydrides



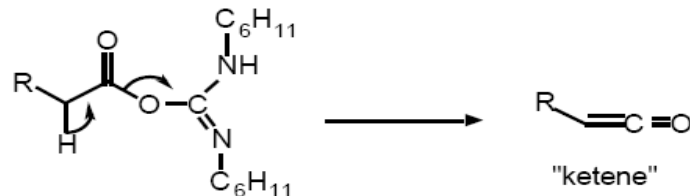
Activating Agents:
Carbonyl Diimidazole



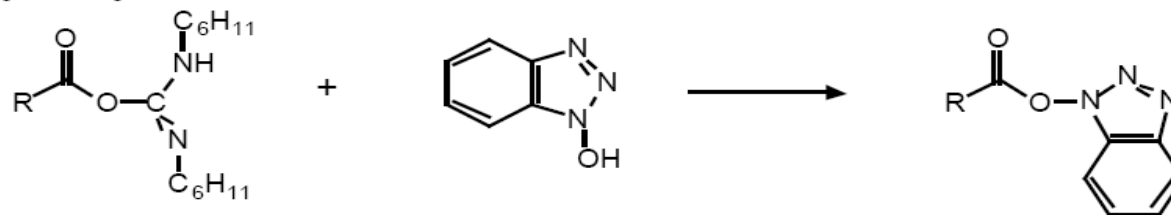
Dicyclohexylcarbodiimide



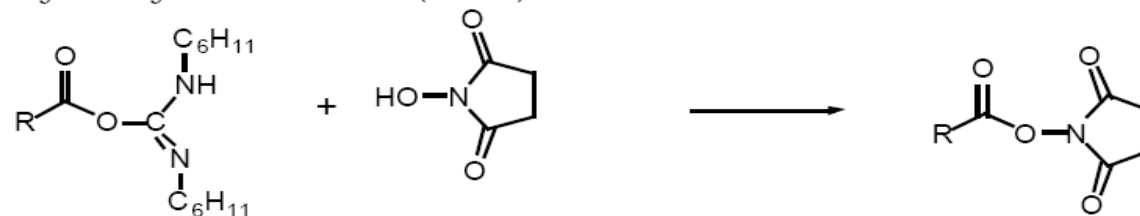
Ketene formation is a common side reaction- scrambling of chiral centers



Hydroxybenzotriazole (HOBT) - reduces ketene formation

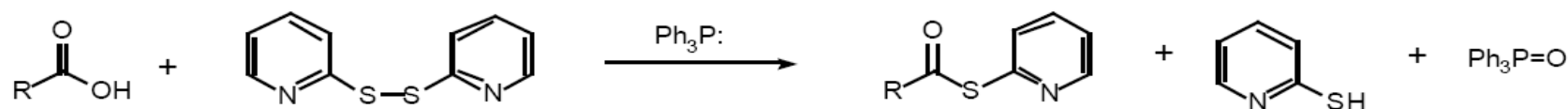


N-Hydroxysuccinimide (NHS)



2,2'-Dipyridyl Disulfide (Aldrithiol, Corey Reagent)

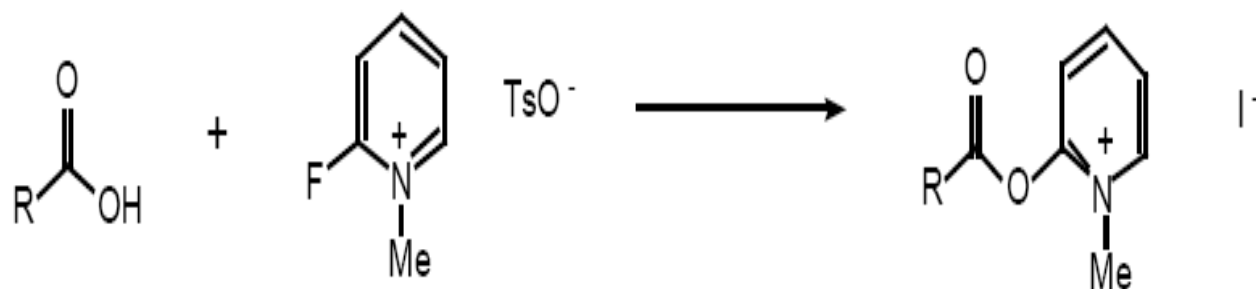
Aldrichimica Acta **1971**, 4, 33



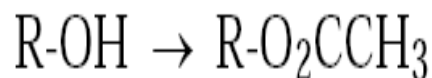
Mukaiyama's Reagent (2-Chloro-1-methyl pyridinium Iodide or 2-Fluoro-1-methyl pyridinium p-toulenesulfonate)

Aldrichimica Acta **1987**, 20, 54

Chem. Lett. **1975**, 1045; 1159; **1976**, 49; **1977**, 575



Acetates



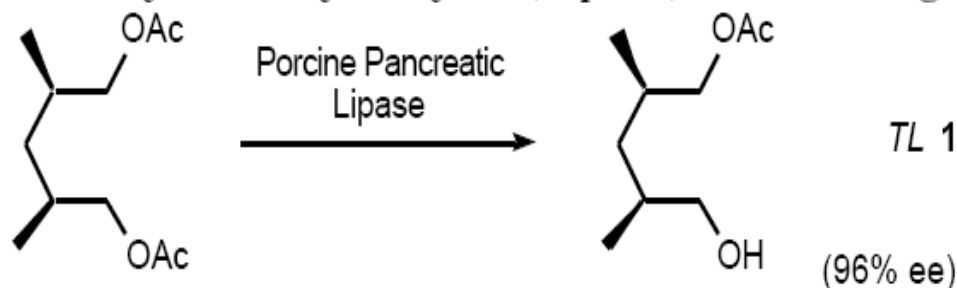
- stable to acid and mild base
- not compatible with strong base or strong nucleophiles such as organometallic reagents

Formation:

- acetic anhydride, pyridine
- acetyl chloride, pyridine

- Cleavage:
- K_2CO_3 , MeOH, reflux
 - KCN, EtOH, reflux
 - NH_3 , MeOH
 - LiOH, THF, H_2O
 - enzymatic hydrolysis (Lipase)

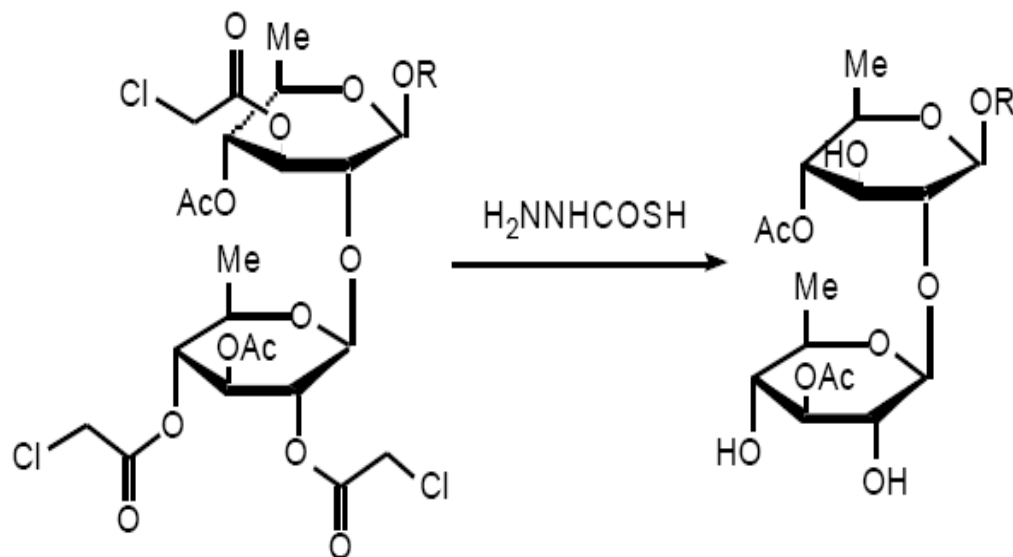
Org. Rxns. **1989**, 37, 1.



TL **1988**, 30, 6189

Chloroacetates

- can be selectively cleaved with Zn dust or thiourea.



JCS CC **1987**, 1026

Trifluoroacetates

Formation: - with trifluoroacetic anhydride or trifluoroacetyl chloride

Cleavage: - K_2CO_3 , MeOH

Pivaloate (t-butyl ester)

- Fairly selective for primary alcohols

Formation: - tbutylacetyl chloride or t-butylacetic anhydride

Cleavage: - removed with mild base

Benzoate (Bz)

- more stable to hydrolysis than acetates.

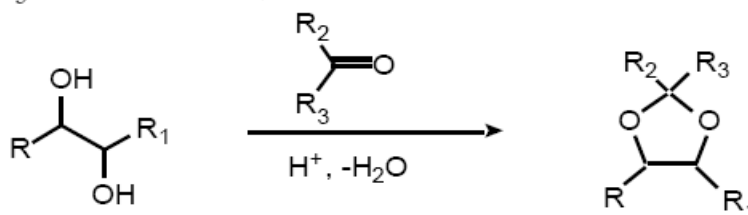
Formation: - benzoyl chloride, benzoic anhydride, benzoyl cyanide (TL 1971, 185), benzoyl tetrazole (TL 1997, 38, 8811)

Cleavage: - mild base
- KCN, MeOH, reflux

1,2 and 1,3- Diols

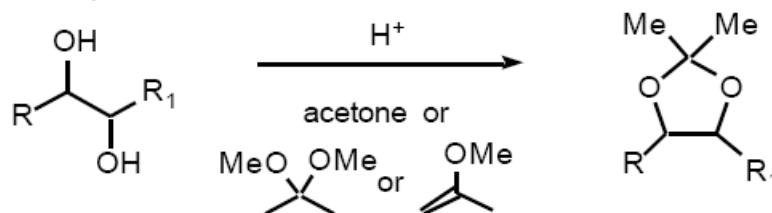
Synthesis 1981, 501

Chem. Rev. 1974, 74, 581



Isopropylidenes

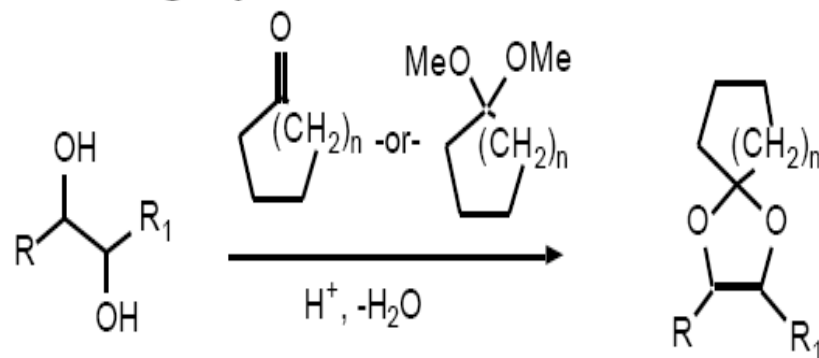
(acetonides)



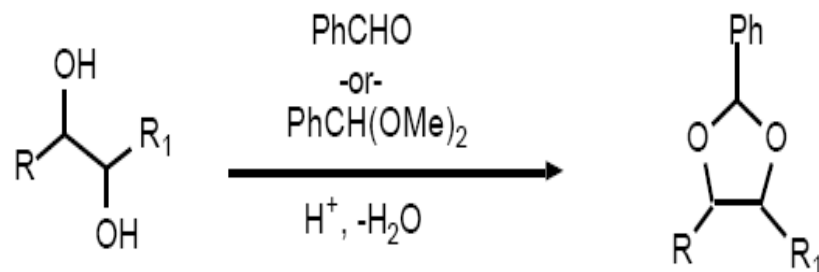
- in competition between 1,2- and 1,3-diols, 1,2-acetonide formation is usually favored
- cleaved with mild aqueous acid

Cycloalkylidene Ketals

- Cyclopentylidene are slightly easier to cleave than acetonides
- Cyclohexylidenes are slightly harder to cleave than acetonides



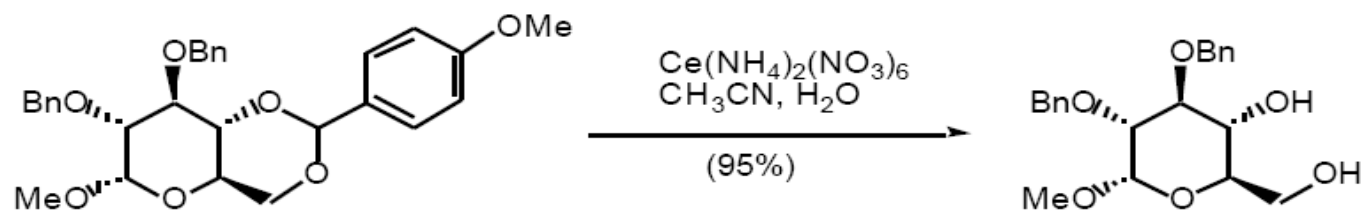
Benzylidene Acetals



- in competition between 1,2- and 1,3-diols, 1,3-benzylidene formation is usually favored
- benzylidenes can be removed by acid hydrolysis or hydrogenolysis
- benzylidenes are usually hydrogenolyzed more slowly than benzyl ethers or olefins.

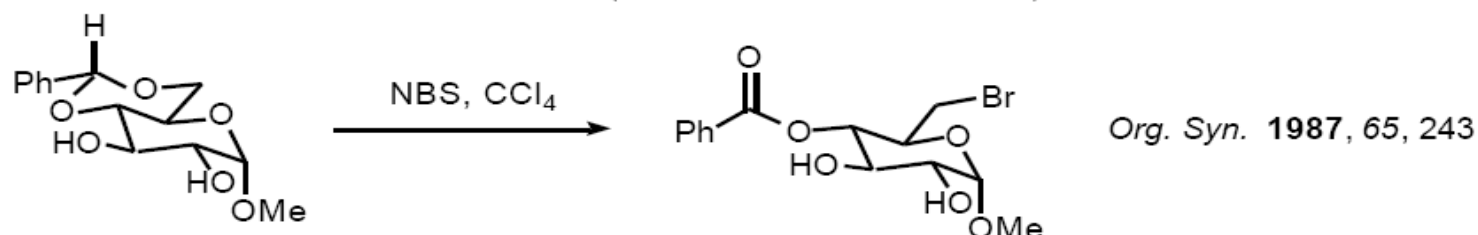
p-Methoxybenzylidenes

- hydrolyzed about 10X faster than regular benzylidenes
- Can be oxidatively removed with $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$ (CAN)



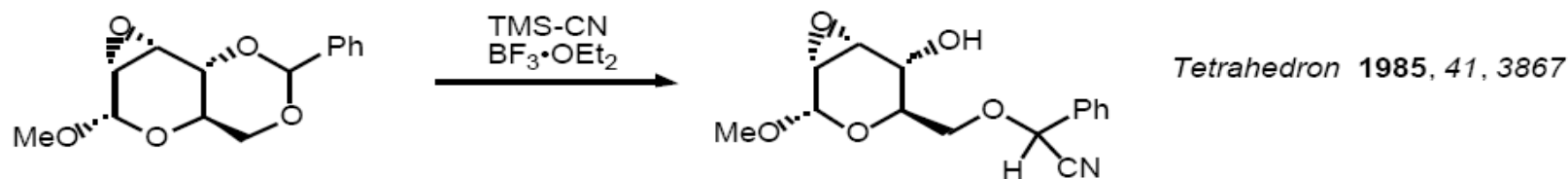
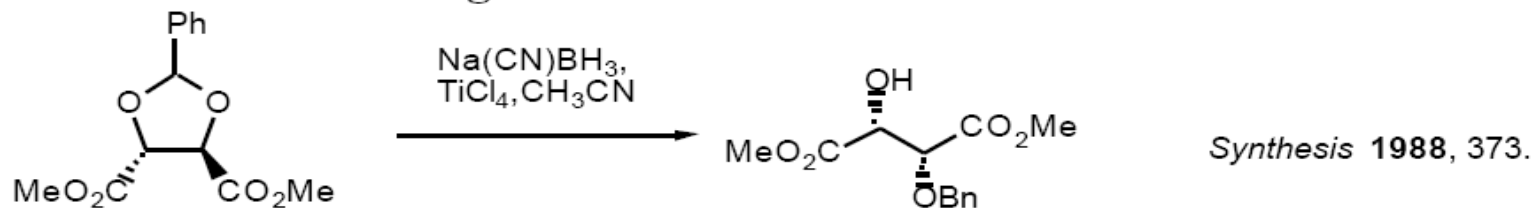
Other Reactions of Benzylidenes

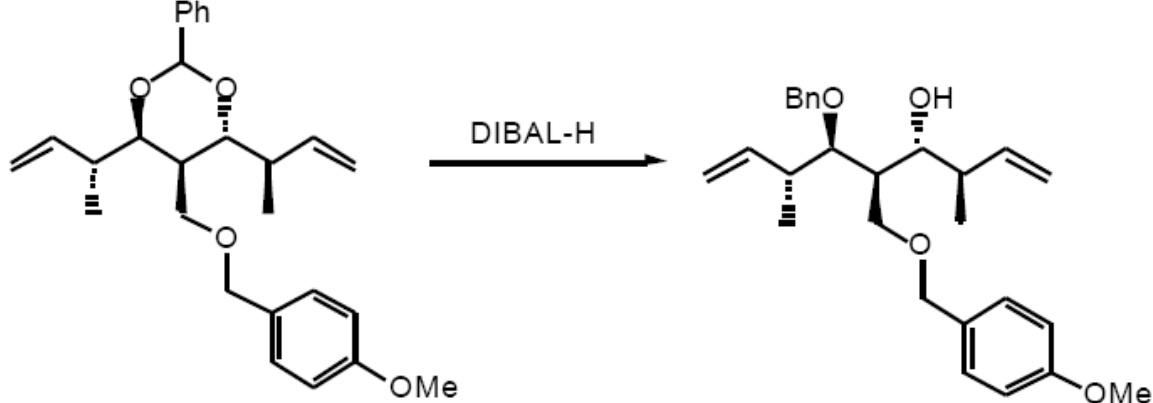
- Reaction with NBS (Hanesian Reaction)



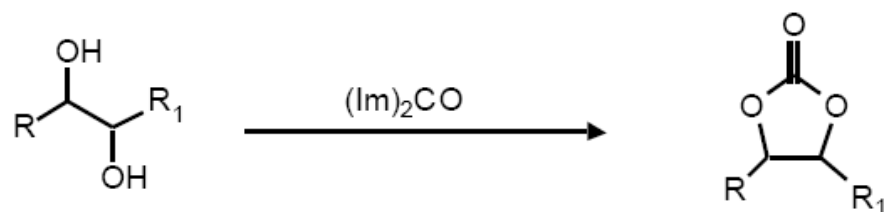
- if benzylidene of a 1° alcohol, then 1° bromide

- Reductive Cleavage





Carbonates

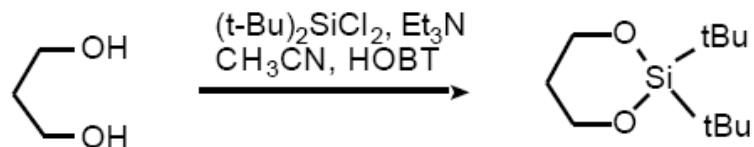


- stable to acid; removed with base
- more difficult to hydrolyze than esters

Di-*t*-Butylsilylene (DTBS)

TL 1981, 22, 4999

- used for 1,3- and 1,4-diols; 1,2-diols are rapidly hydrolyzed
- cleaved with fluoride (HF, CH₃CN -or- Bu₄NF⁻ -or- HF • pyridine)
- will not functionalize a 3°-alcohol



1,3-(1,1,3,3)-tetraisopropylidisiloxanylidene (TIPDS)

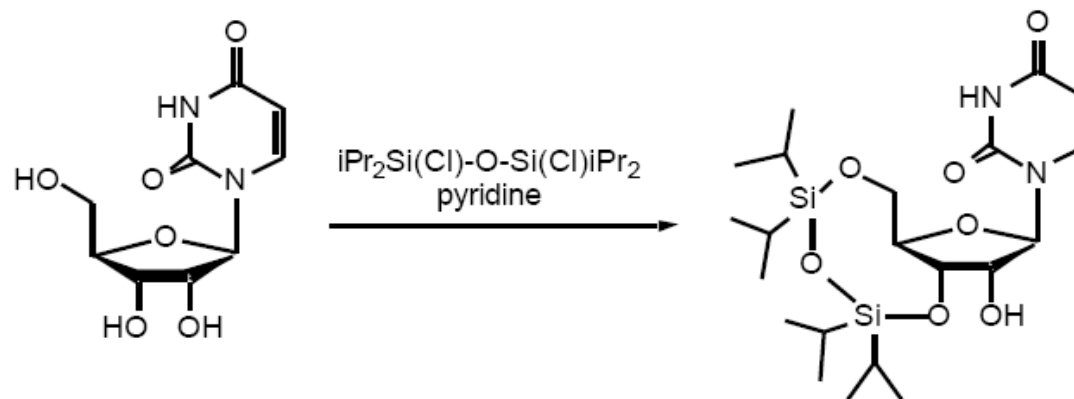
TL 1988, 29, 1561

- specific for 1,3- and 1,4-diols
- cleaved with fluoride or TMS-I

1,3-(1,1,3,3)-tetraisopropyldisiloxanylidene (TIPDS)

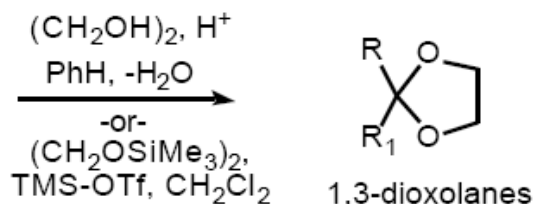
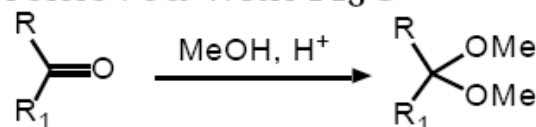
TL 1988, 29 , 1561

- specific for 1,3- and 1,4-diols
- cleaved with fluoride or TMS-I



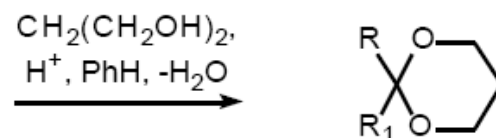
Ketones and Aldehydes

- ketones and aldehydes are protected as cyclic and acyclic ketals and acetals
- Stable to base; removed with H_3O^+



TL 1980, 21 , 1357

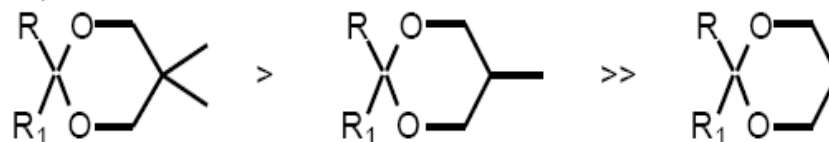
1,3-dioxolanes



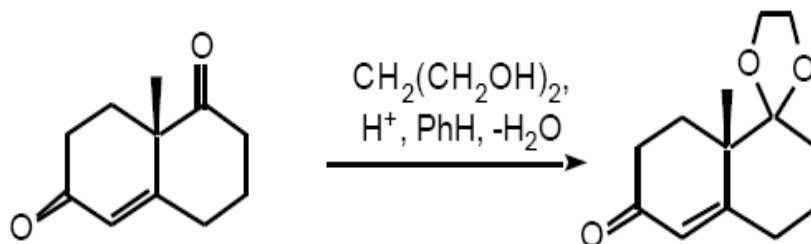
1,3-dioxanes

Cleavage rate of substituted 1,3-dioxanes:

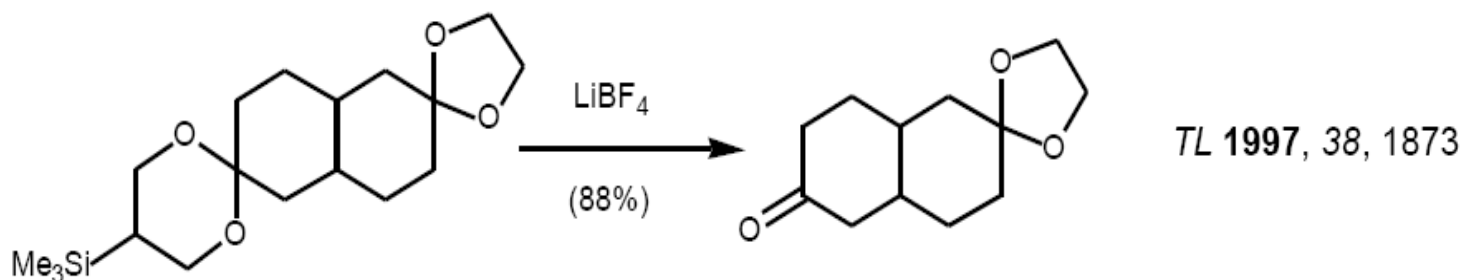
Chem. Rev. **1967**, 67, 427.



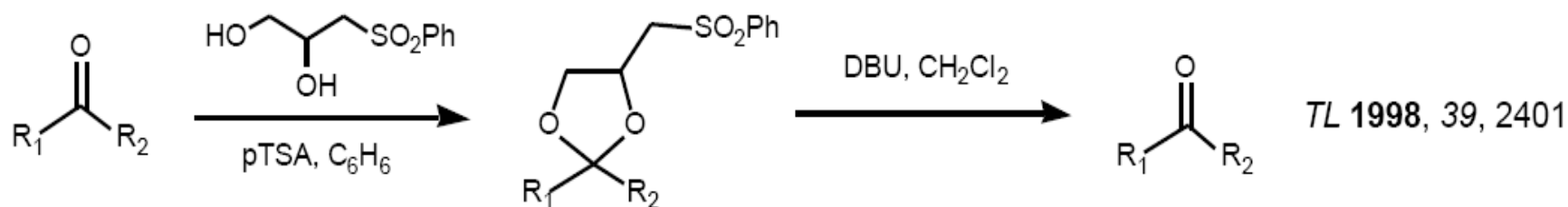
- Ketal formation of α,β -unsaturated carbonyls are usually slower than for the saturated case.

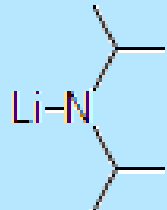


Fluoride cleavable ketal:



Base cleavable ketal:

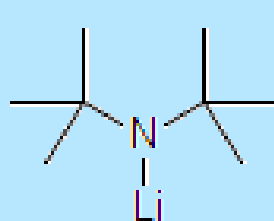




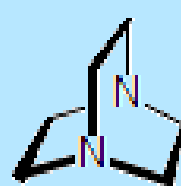
LDA



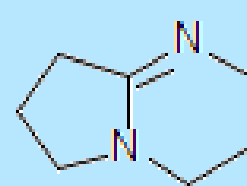
K-HMDS



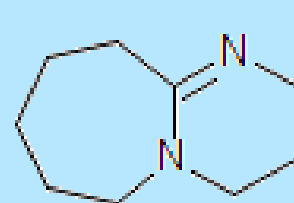
LiTMP



DABCO



DBN



DBU

Carboxylic Acids

Tetrahedron **1980**, 36, 2409. *Tetrahedron* **1993**, 49, 3691

Nucleophilic Ester Cleavage:

Organic Reactions **1976**, 24, 187.

Esters

Alkyl Esters

formation: - Fisher esterification ($\text{RCOOH} + \text{R}'\text{OH} + \text{H}^+$)

- Acid Chloride + R-OH , pyridine

- t-butyl esters: isobutylene and acid

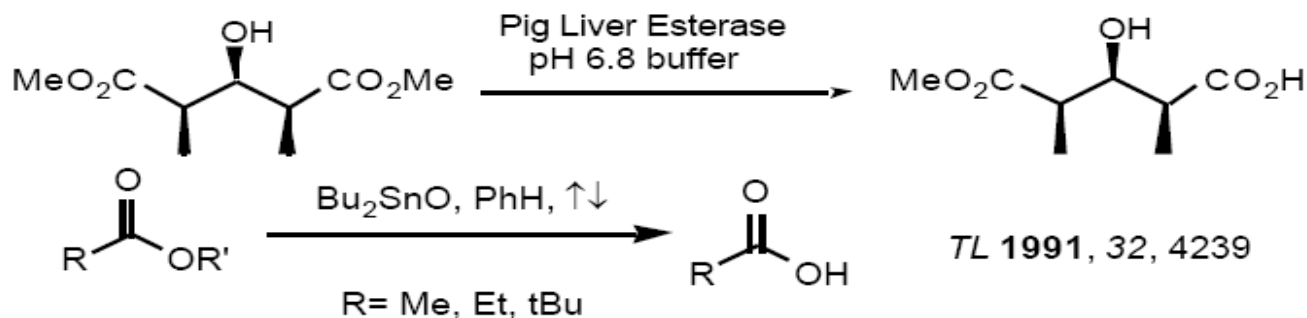
- methyl esters: diazomethane

Cleavage: - LiOH , THF, H_2O

- enzymatic hydrolysis *Org. Rxns.* **1989**, 37, 1.

- t-butyl esters are cleaved with aqueous acid

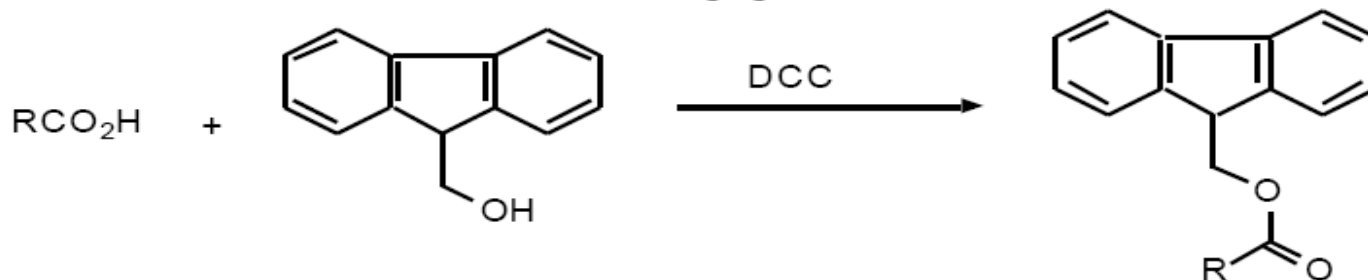
- Bu_2SnO , PhH, reflux (TL **1991**, 32, 4239)



9-Fluorenylmethyl Esters (Fm)

TL **1983**, 24, 281

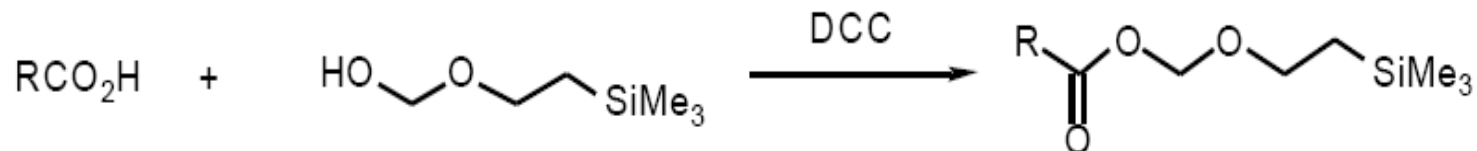
- cleaved with mild base (Et_2NH , piperidine)



2-(Trimethylsilyl)ethoxymethyl Ester (SEM)

HCA **1977**, 60, 2711.

- Cleaved with Bu_4NF in DMF

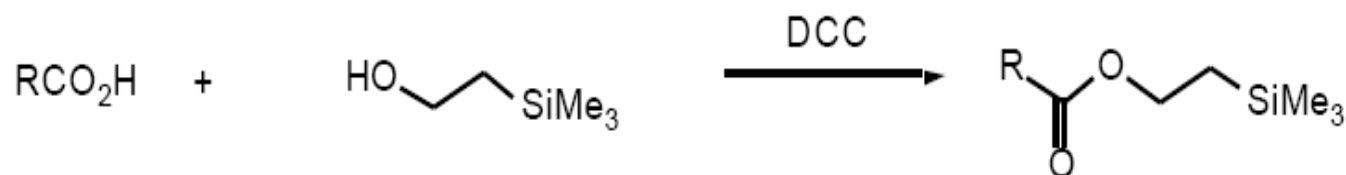


- Cleaved with $\text{MgBr}_2 \cdot \text{OEt}_2$ TL **1991**, 32, 3099.

2-(Trimethylsilyl)ethyl Esters

JACS **1984**, 106, 3030

- cleaved with Fluoride ion

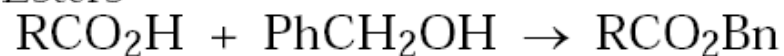


Haloesters

- cleaved with $\text{Zn}(0)$ dust or electrochemically



Benzyl Esters



Formation:

- DCC
- Acid chloride and benzyl alcohol

Cleavage:

- Hydrogenolysis
- Na, NH₃

Diphenylmethyl Esters



Cleavage:

- mild H₃O⁺
- H₂, Pd/C
- BF₃•OEt₂

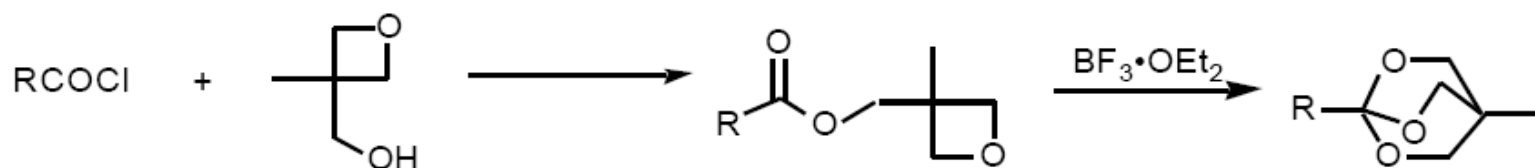
o-Nitrobenzyl Esters

- selective removed by photolysis

Orthoesters *Synthesis* **1974**, 153

TL **1983**, 24, 5571

Chem. Soc. Rev. **1987**, 75



- Stable to base; cleaved with mild acid

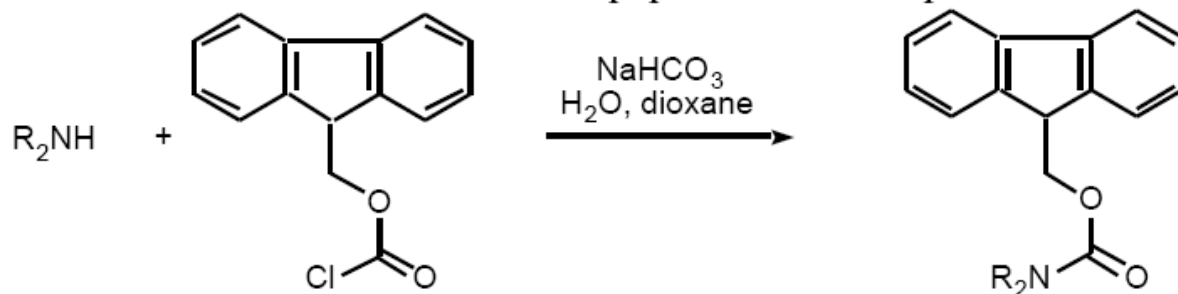
Amines

Carbamates

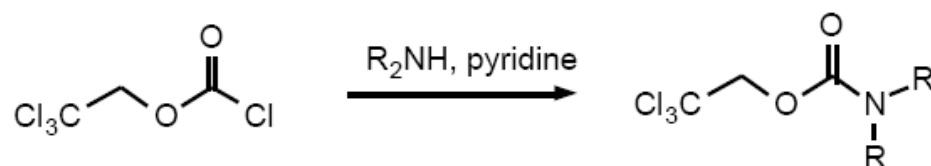
9-Fluorenylmethyl Carbamate (Fmoc)

Acc. Chem. Res. **1987**, *20*, 401

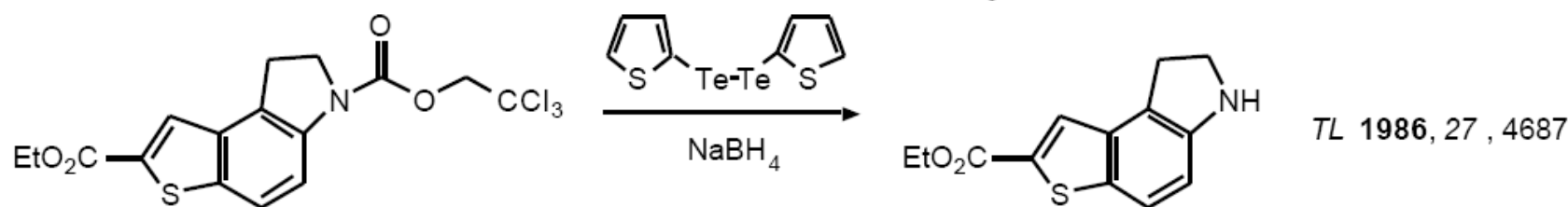
- Cleaved with mild base such as piperidine, morpholine or dicyclohexylamine



2,2,2-Trichloroethyl Carbamate

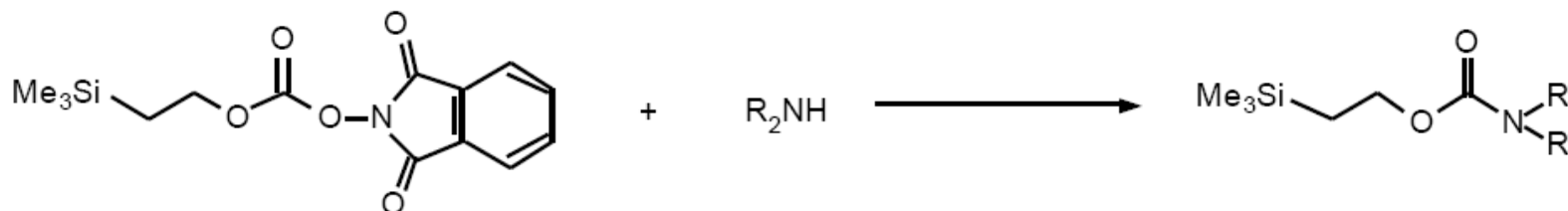


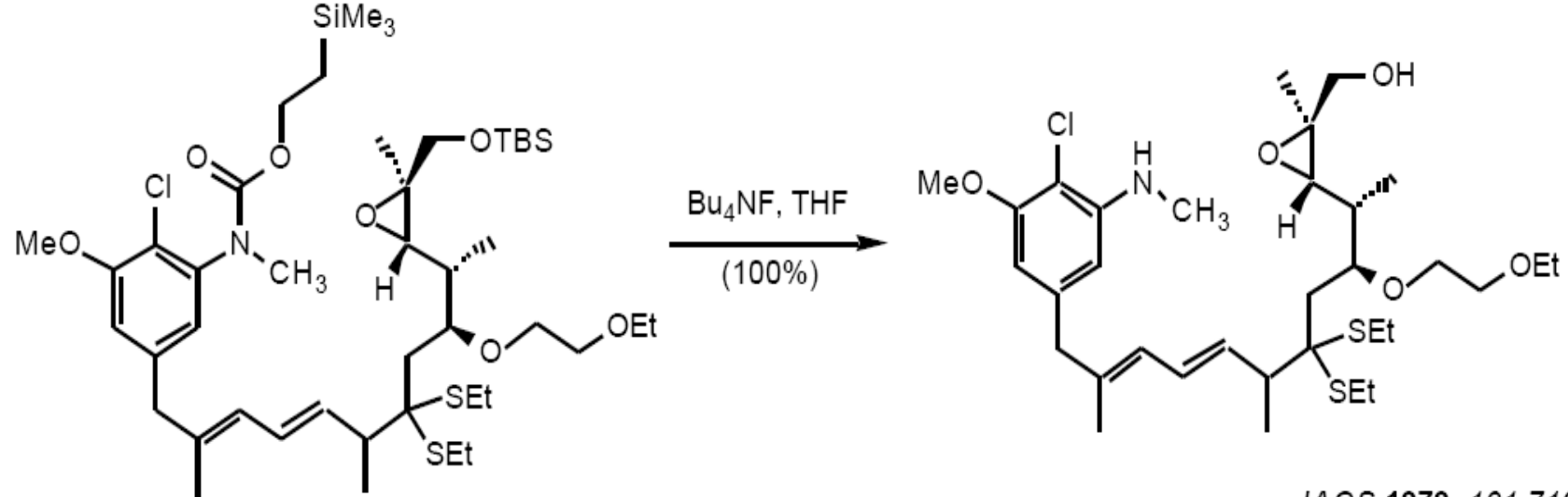
- Cleaved with zinc dust or electrochemically.



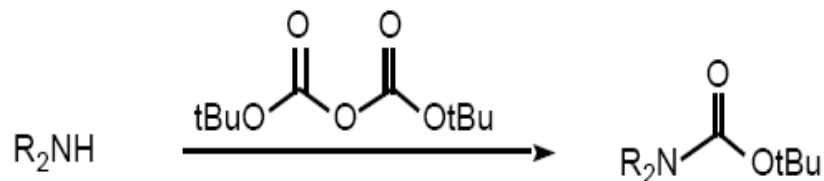
2-Trimethylsilylethyl Carbamate (Teoc)

- cleaved with fluoride ion.



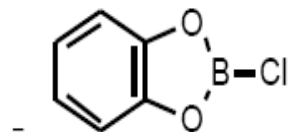


t-Butyl Carbamate (BOC)



Cleavage:

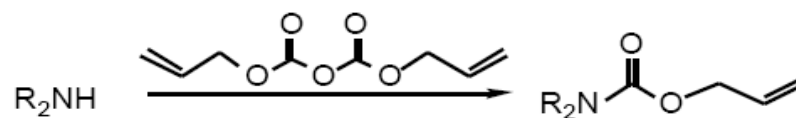
- with strong protic acid (3M HCl, CF₃COOH)
- TMS-I



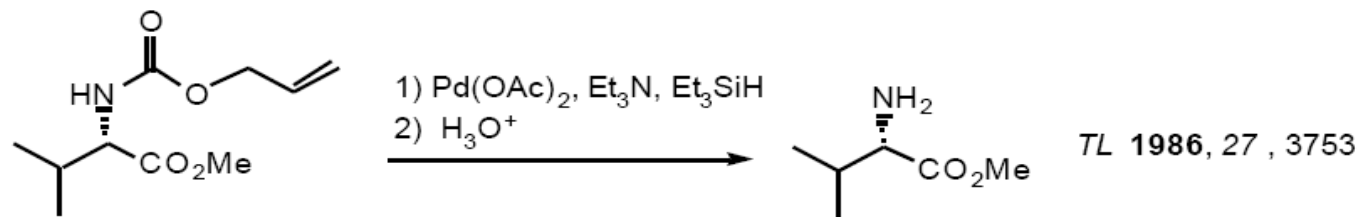
TL 1985, 26, 1411

Allyl Carbamate (Alloc)

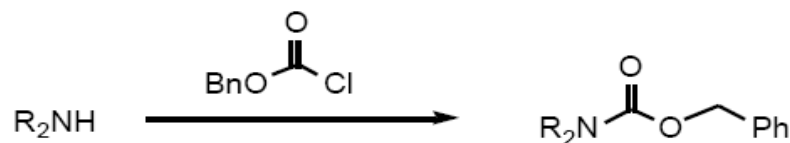
TL 1986, 27, 3753



- removed with Pd(0) and a reducing agent (Bu₃SnH, Et₃SiH, HCO₂H)



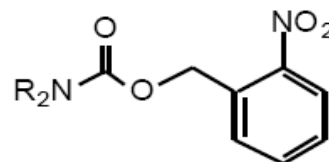
Benzyl Carbamate (Cbz)



Cleavage:

- Hydrogenolysis
- PdCl₂, Et₃SiH
- TMS-I
- BBr₃
- hv (254 nm)
- Na/ NH₃

m-Nitrophenyl Carbamate
JOC 1974, 39, 192

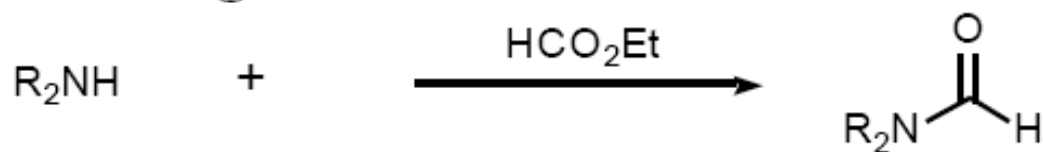


- removed by photolysis

Amides

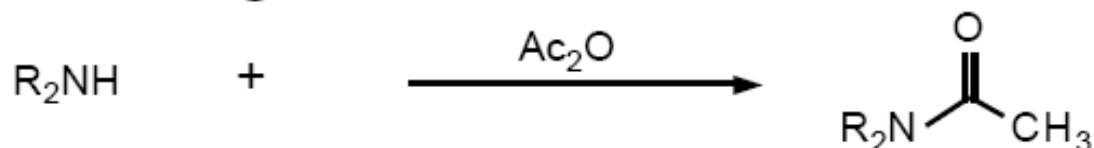
Formamides

- removed with strong acid



Acetamides

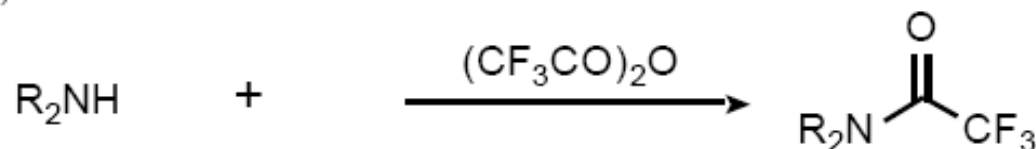
- removed with strong acid



Trifluoroacetamides

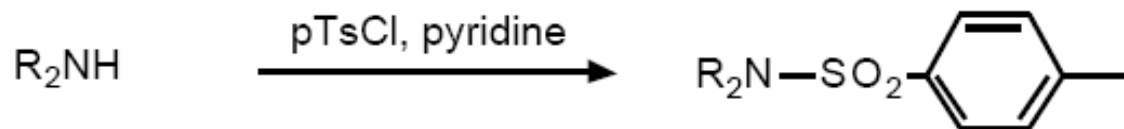
Cleavage:

- base (K_2CO_3 , MeOH, reflux)
- NH_3 , MeOH



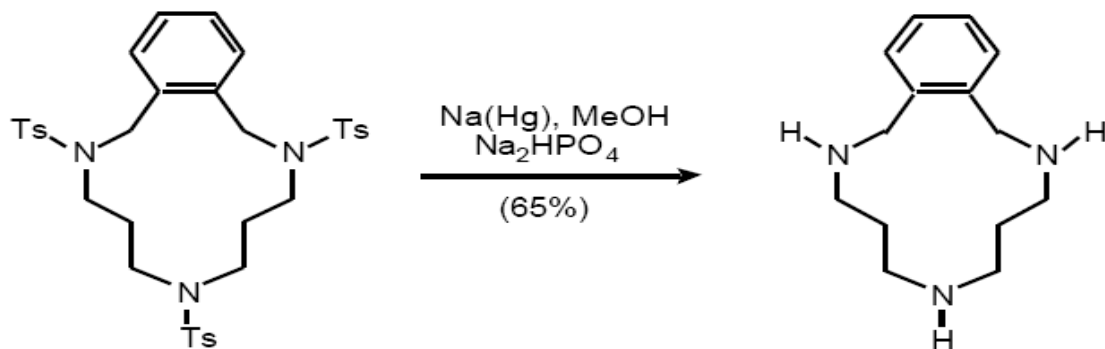
Sulfonamides

p-Toluenesulfonyl (Ts)



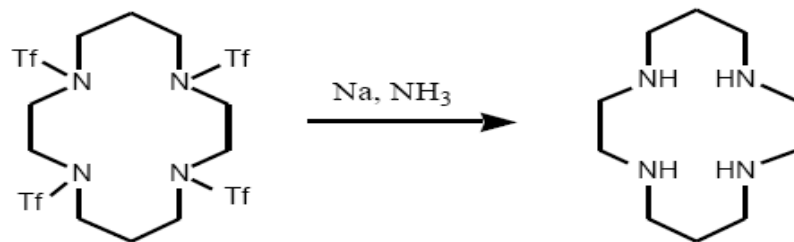
Cleavage:

- Strong acid
- sodium Naphthalide
- Na(Hg)



JOC 1989, 54, 2992

Trifluoromethanesulfonyl

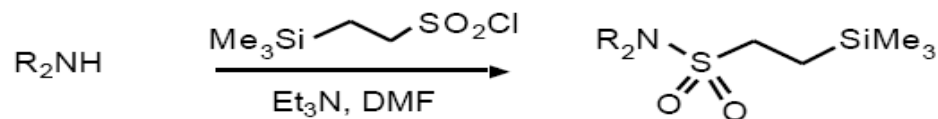


JOC 1992, 33, 5505

Trimethylsilylethanesulfonamide (SES)

TL 1986, 54, 2990; *JOC* 1988, 53, 4143

- removed with CsF, DMF, 95°C



tert-Butylsulfonyl (Bus) *JOC* 1997, 62, 8604

